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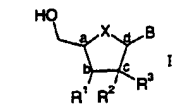
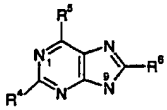
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,

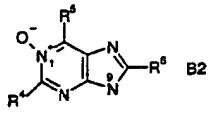
[Continued on next page]

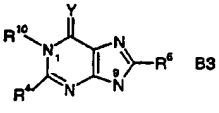
(54) Title: NUCLEOSIDE DERIVATIVES FOR THE TREATMENT OF HEPATITIS C

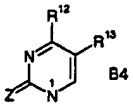
Use of compounds of formula I

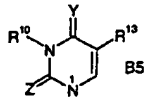












(57) Abstract: Use of compounds of formula (I), wherein R^1 is hydrogen, hydroxy, alkyl, hydroxyalkyl, alkoxy, halogen, cyano, isocyano or azido; R^2 is hydrogen, hydroxy, alkoxy, chlorine, bromine or iodine; R^3 is hydrogen; or R^2 and R^3 together represent $=CH_2$; or R^2 and R^3 represent fluorine; X is O, s or CH_2; a, b, c, d denoting asymmetric carbon atoms each of which is substituted with 4 different substituents; and B signifies a purine base B1 which is connected through the 9-nitrogen of formula (B1), wherein R^4 is hydrogen, hydroxyl, alkyl, alkoxy, alkylthio, aryloxy, arylthio, heterocyclyl, NR^7R^8, halogen or SH; R^5 is hydrogen, hydroxy, alkyl, haloalkyl, cycloalkyl, alkoxy, alkylthio, aryl, aryloxy, arylthio, heterocyclyl, heterocyclylamino, halogen, NR^7R^8, $NHOR^9$, $NHNR^7R^8$ or SH; R^6 is hydrogen, hydroxy, alkyl, alkoxy, alkylthio, aryloxy, arylthio, heterocyclyl, NR^7R^8, halogen, SH or cyano; R^7 and R^8 are independently of each other hydrogen, alkyl, aryl, hydroxyalkyl, alkenylalkyl, alkynylalkyl, cycloalkyl or acyl; R^9 is hydrogen, alkyl or aryl; or B signifies an oxidised purine base B2 which is connected through the 9-nitrogen of formula (B2), wherein R^4, R^5 and R^6 are as defined above; or B signifies a purine base B3 which is connected through the 9-nitrogen of formula (B3), wherein R^4 and R^6 are as defined above; R^{10} is hydrogen, alkyl or aryl; Y is O, S or NR^{11}; R^{11} is hydrogen, hydroxy, alkyl, OR^9, heterocyclyl or NR^7R^8; R^7, R^8 and R^9 are as defined above; or B signifies a pyrimidine base B4 which is connected through the 1-nitrogen of formula (B4), wherein Z is O or S; R^{12} is hydrogen, hydroxy, alkyl, alkoxy, haloalkyl, alkylthio, aryl, aryloxy, arylthio, heterocyclyl, heterocyclylamino, halogen, NR^7R^8, $NHOR^9$, $NHNR^7R^8$ or SH; R^{13} is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, haloalkyl, cycloalkyl or halogen; R^7, R^8 and R^9 are as defined above; or B signifies a pyrimidine base B5 which is connected through the 1-nitrogen of formula (B5), wherein Y, Z, R^{10} are as defined above for the treatment of diseases mediated by the Hepatitis C Virus (HIV) or for the preparation of a medicament for such treatment. The invention is concerned with novel and known purine and pyrimidine nucleoside derivatives, their use as inhibitors of subgenomic Hepatitis C Virus (HCV) RNA replication and pharmaceutical compositions of such compounds.

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CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

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Published:

— *with international search report*

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14 November 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/09633

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H19/06 C07H19/16 A61K31/7064 A61K31/7076 A61P31/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07H A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 98 16184 A (ICN PHARMACEUTICALS ;AVERTT DEVERON (US); TAM ROBERT (US); WANG GU) 23 April 1998 (1998-04-23) examples claims page 11, line 14 ---	1,15,16
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 July 2002	26. 07. 2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	de Nooy, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 01/09633

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 55 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.

2. [X] Claims Nos.: 43,49-57 (all partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT, no additional fees are to be refunded.

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[X] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 43,49-57 (all partially)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty for claim 43. So many documents were retrieved that it is impossible to determine which parts of the claim may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, it appears impossible to execute a meaningful search and/or to issue a complete search report over the whole breadth of the claims. Consequently, the search and the report for this claim has been restricted to the case where R13'''''' is an alkyl but not methyl.

Present claims 49-57 relate to an extremely large number of compounds. In fact, the claims contain so many options, that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the above mentioned claims have been searched insofar as the compounds of claim 49 fall within earlier compound claims.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1 (in part), 3-4 (in part), 12-13 (in part), 14, 34, 35, 50-56 (in part)

   Compounds of Formula I-a of claim 34 where B' = B2-a of claim 34, and uses, compositions and processes pertaining thereto.

2. Claims: 1 (in part), 3-4 (in part), 15-16 (in part), 17, 36, 37, 50-56 (in part)

   Compounds of Formula I-b of claim 36 where B'' = B3-a of claim 36, and uses, compositions and processes pertaining thereto.

3. Claims: 1-4 (in part), 18-25 (in part), 26, 27-28 (in part), 29, 38-42, 50-56 (in part)

   Compounds of Formula I-c of claim 38 where B''' = B4-a of claim 38, compounds of Formula I-d of claim 40 where B'''' = B4-b of claim 40 or 41, and uses, compositions and processes pertaining thereto.

4. Claims: 1-4 (in part), 30-32 (in part), 33, 43-48, 50-56 (in part)

   Compounds of Formula I-e of claim 43 where B''''' = B5-a of claim 43, compounds of Formula I-f of claim 45 where B'''''' = B5-b of claim 45, compounds of Formula I-g of claim 47 where B''''''' = B5-c of claim 47 and uses, compositions and processes pertaining thereto.

5. Claims: 1-4 (in part), 5-10, 12-13 (in part), 15-16 (in part), 18-25 (in part), 27-28 (in part), 30-32 (in part), 55-56 (in part)

   Use of compounds of the above mentioned claims which do not fall within one of the previous subjects for the treatment of Hepatitis C Virus or for the preparation of a medicament for such treatment.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/09633

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 05687 A (UNIV BIRMINGHAM ;WELLCOME FOUND (GB); MILLER JOHN ALLEN (GB); YOUN) 17 March 1994 (1994-03-17) examples claims page 4, line 22 - line 36	1,2, 30-32
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X	US 5 102 873 A (MONTGOMERY JOHN A ET AL) 7 April 1992 (1992-04-07) example 3	34
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A	US 5 998 387 A (SCAMMELLS PETER J ET AL) 7 December 1999 (1999-12-07) figure 2	34
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	H. VORBRÜGGEN ET AL.: "Eine neue einfache Synthese von Cytidinen" LIEBIGS ANN. CHEM., 1975, pages 988-1002, XP002204034 compound 19	38
X	X.-X. ZHOU ET AL.: "Pyridyl groups for protection of the imide functions of uridine and guanosine. Exploration of their displacement reactions for site-specific modifications of uracil and guanine bases" ACTA CHEMICA SCANDINAVICA B, vol. 40, 1986, pages 806-816, XP002204035 the whole document	38
X	R.W. MILES ET AL.: "Nucleic acid related compounds. 87. Nucleophilic functionalization of cytidine and 2'-deoxycytidine derivatives via elaboration of the 4-amino group into a readily displaced 1,2,4-triazol-4-yl substituent" J. ORG. CHEM., vol. 60, 1995, pages 7066-7069, XP002204036 compounds 3,4	38
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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X	KOTRA L P ET AL: "STRUCTURE-ACTIVITY RELATIONSHIPS OF 2'-DEOXY-2',2'-DIFLUORO-L-ERYTHRO-PENTOFURANOSYL NUCLEOSIDES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 40, no. 22, 1997, pages 3635-3644, XP000867642 ISSN: 0022-2623 compounds 43-52 ---	40
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X	M. SEKINE, T. NAKANISHI: "Facile synthesis of 3'-O-methylthymidine and 3'-deoxythymidine and related deoxygenated thymidine derivative: A new method for selective deoxygenation of secondary hydroxy groups" J. ORG. CHEM., vol. 55, 1990, pages 924-928, XP002204038 compound 2 ---	43
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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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International Application No
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